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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/729,387
Filing Date: December 08, 2003
Appellant(s): GILES ET AL.

Brion P. Heaney
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/16/2008 appealing from the Office action mailed 1/16/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 96/07413, Published March 14, 1996;

Giles *et al.* "Troxacitabine, A Novel Dioxolane Nucleoside Analog, Has Activity in Patients with Advanced Leukemia" Journal of Clinical Oncology, vol. 19, no. 3 (February 1), 2001, pages 762-771;

Druker *et al.* "Activity of a Specific Inhibitor of the BCR-ABL Tyrosine Kainse in the Blast Crisis of Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia with the Philadelphia Chromosome" The New England Journal of Medicince, vol. 344, no. 14 (April 5, 2001), pages 1038-1042;

Fang *et al.* "CGP57148B (STI-571) Induces Differentiation and Apoptosis and Sensitizes Bcr-Abl-positive Human Leukemia Cells to Apoptosis Due to Antileukemic Drugs" Blood, vol. 96, no. 6 (Sept. 15, 2000), pages 2246-2253; and

Topaly *et al.* "Synergistic Activity of the New ABL-specific Tyrosine Kinase Inhibitor STI-571 and Chemotherapeutic Drugs on BCR-ABL-positive chronic myelogenous leukemia cells" Leukemia, vol. 15, 2001, pages 342-347.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 9-10, 14-15, 17-22, 25-32, 39-45 and 52-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Chu *et al.*** (WO 96/07413), **Giles *et al.*** (JCO, 2001) and **Druker *et al.*** (N. Engl. J. Med., 2001, vol. 344, pages 1038-1042) in view of **Fang *et al.*** (Blood, 2000, vol. 96, pages 2246-2253) and **Topaly *et al.*** (Leukemia, 2001) (all prior art of record).

The instant claims are drawn to compositions comprising L-(-)-OddC (troxacitabine) and imatinib mesylate (STI-571) and methods of treating leukemia with said compositions.

Troxacitabine is well known in the art as a treatment for leukemia and is preferably used as its (-) enantiomer. For example, Chu *et al*. disclose the use of (-)-(*2S,4S*)-L-(2-hydroxymethyl-1,3-dioxolan-4-yl)cytosine (also referred to as (-)-OddC, L-OddC, (-)-L-OddC, or troxacitabine) in the treatment of cancer (page 5, lines 17-27; page 47, Claim 12). The compounds disclosed in Chu et al. are the same compounds recited as formula (I) in the instant

claims. The compound is administered as it's substantially (-) enantiomer (*i.e.* free of the (+) enantiomer) (page 6, lines 6-11). Chu *et al.* define "enantiomerically enriched" to refer to a nucleoside composition that includes at least approximately 95%, and preferably approximately 97%, 98%, 99%, or 100% of a single enantiomer of that nucleoside, thus teaching the limitations of claims 9, 10, 31 and 32. In a preferred embodiment, (-)-L-OddC or its derivative or salt is provided in a nucleoside composition that consists essentially of one enantiomer, *i.e.*, as the indicated enantiomer (the L-enantiomer) and substantially in the absence of its corresponding D-enantiomer (*i.e.*, in enantiomerically enriched, including enantiomerically pure form) (page 11, lines 6-18). Leukemia is recited as one type of cancer (-)-L-OddC can be used to treat (page 6, lines 22-28), thus suggesting the treatment of leukemia with (-)-L-OddC as recited in the instant claims. It is further disclosed that (-)-L-OddC can be administered in combination with other anticancer agents, including interferons, interleukins and cytarabine (page 7, line 21 to page 8, line 20), thus suggesting combination therapy as recited in the instant claims. Figure 3 shows the results of treatment of P388 (an experimental lymphocytic leukemia cell line) leukemic mice with (-)-L-OddC. Further, the *in vitro* activity of (-)-L-OddC was demonstrated against several different leukemia cell lines (Table 2, page 35).[1] These tested leukemia cell lines correspond to an acute lymphoblastic cell line (CCRF-CEM), an acute promyelocytic leukemia cell line (HL-60), a chronic myelogenous leukemia (CML) cell line (K-562) and an acute lymphoblastic leukemia cell line (MOLT-4).

[1] It is noted that the leukemia cell lines in Table 2 are not properly identified. It is believed that RL-60(TB) is HL-60; BSOLT-4 is MOLT-4; and RPMI-2.26 is RPMI-82.26.

Giles *et al.* is provided to show that the instantly claimed doses of (-)-L-OddC for the treatment of leukemia were known in the art. (-)-L-OddC (troxacitabine) is disclosed as being effective in the treatment of refractory or relapsed acute myeloid leukemia (AML) or lyphocytic (ALL) leukemia, myelodysplastic syndromes (MDS) or chronic myelogenous leukemia in blastic phase (CML-BP) (see especially Abstract). Troxacitabine was administered to patients in doses of 0.72 to 10 mg/m^2/day (page 765, Table 3), thus suggesting the doses of (-)-L-OddC as recited in claims 39 and 40. The MTD was determined to be 8 mg/m^2/day (Abstract).

Druker *et al.* is provided to show that the instantly claimed doses of imatinib mesylate (STI-571) for the treatment of leukemia were known in the art. STI-571 is a specific inhibitor of the Bcr-Abl tyrosine kinase and has been used to treat CML in blast crisis as well as ALL with the Philadelphia chromosome (*i.e.* ALL expressing Bcr-Abl) (see especially Abstract). Bcr-Abl is present in virtually all cases of CML and in 20% of cases of ALL. STI-571 was given orally at daily doses ranging from 300 to 1000 mg (Abstract; page 1040, Tables 4 & 5), thus suggesting the doses of STI-571 as recited in claims 39 and 40.[2]

Neither Chu *et al.*, Giles *et al.* nor Druker *et al.* disclose the specific combination of troxacitabine and imatinib mesylate, although Chu *et al.* does suggest that (-)-L-OddC can be combined with other chemotherapeutic agents (page 7, line 21 to page 8, line 20). Further, as Applicants acknowledge at pages 2-3 of the instant specification, combinations of two or more drugs are routinely administered as treatment for leukemia (*e.g.*, page 2, lines 4-15). In fact, as

[2] The average male has a body surface area of 1.9 m^2, the average female, 1.6 m^2. Thus, the doses administered correspond to 0.16 g/m^2 to 0.53 g/m^2/d (males) and 0.19 g/m^2 to 0.63 g/m^2/d (females).

further acknowledged by Applicants, STI-571 has been previously combined with other chemotherapeutics in the treatment of leukemia (page 3, lines 4-9).

Fang *et al.* and Topaly *et al.* provide further motivation to combine STI-571 with other chemotherapeutic drugs wherein they disclose that combined therapies comprising STI-571 and other antileukemic drugs are synergistic when used to treat Bcr-Abl-positive human leukemia. For example, Fang *et al.* disclose that STI-571 induces hemoglobin levels and apoptosis of K562 and HL-60/Bcr-Abl leukemia cells (page 2249, right column). Co-treatment with STI-571 significantly increased the percentage of apoptotic cells following exposure to Ara-C or doxorubicin (Table 2). This effect was not observed in HL-60/neo cells, which do not express Bcr-Abl and are highly sensitive to apoptosis induced by Ara-C and doxorubicin (page 2251, left column). As conventional chemotherapy with Ara-C, doxorubicin and etoposide does not have major clinical efficacy against Bcr-Abl-positive acute leukemia or the blast crisis of CML, the data presented suggest that the effects of STI571 on these leukemias "may sensitize Bcr-Abl-positive human leukemic cells to apoptosis induced by antileukemic drugs" (page 2252, right column, last paragraph).

Further evidence of such synergism is found in Topaly *et al.* wherein STI-571 is demonstrated to have a synergistic effect when administered with other chemotherapeutic drugs on Bcr-Abl-positive CML cells (Abstract; Figure 2). The data provided therein implies that:

> "STI571 exhibits strong synergism with apoptosis-inducing cytarabine, mafosfamide and etoposide at higher levels of growth inhibition, which may originate from increasing inhibition of the BCR-ABL tyrosine kinase with subsequent induction of apoptotic pathways by these chemotherapeutic drugs" (page 346, right column).

Thus, the reference provides one skilled in the art with the motivation and reasonable expectation of success in treating Bcr-Abl-positive CML with a combination therapy of STI-571 and other chemotherapeutic agents.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art is replete with examples of chemotherapeutic agents being combined to treat cancer, including leukemia. In fact, combination chemotherapy has become commonplace in the treatment of cancer. Applicants acknowledge that the instantly claimed compounds have been previously used to treat leukemia and further acknowledge that STI-571 has been combined with other chemotherapeutic agents for the treatment of leukemia. The prior art also discloses methods of administration and doses of the instantly claimed compounds that can be used in the treatment of leukemia.

The prior art differs from the instant claims in that it does not explicitly teach the specific combination of chemotherapeutic agents instantly claimed. However, one of ordinary skill in the art (in this case, an M.D. with several years of experience) would have been highly motivated to

combine two known antileukemic agents for the treatment of leukemia. As noted *supra*, such combinations are well known, in fact routine, in the art.

Accordingly, the instantly claimed formulations and methods of treating leukemia with a combination of (-)-L-OddC and imatinib mesylate would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The prior art discloses that both of these agents can be used to treat leukemia in the doses instantly claimed and further demonstrates that STI-571 has a synergistic effect when combined with other chemotherapeutic agents in the treatment of CML. As such, the skilled artisan has been provided with the explicit teaching that STI-571 can be combined with other chemotherapeutics and would be imbued with more than a reasonable expectation that such a combination would be effective (and likely synergistic) in the treatment of CML or other leukemias wherein Bcr-Abl is expressed (*e.g.* ALL). Further, in the absence of a showing of the criticality of the instantly claimed ratios of (-)-L-OddC to STI-571, such ratios would have been obvious to one of ordinary skill in the art and readily determined through routine optimization.

The motivation to combine the above references is explicitly found in Fang and Topaly as stated above. Moreover, (-)-L-OddC and STI-571 (*i.e.* imatinib mesylate) are individually known in the art as agents for treating leukemia, whose efficacy when administered alone is well established for the treatment of different leukemia types. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q.

1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

It is not inventive to take two well-known antileukemia agents and combine them for the treatment of the same leukemias for which they are individually known in the art to be effective in treating. As evidenced by the prior art and Applicants' admissions in the specification, such combination chemotherapy is routine in the art of treating cancer. Accordingly, to establish obviousness in such fact situations it is not necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Accordingly, the claims are deemed properly rejected as being an obvious modification of the prior art.

(10) Response to Argument

Appellants argue that the cited references do not disclose or suggest treating leukemia with a combination of (-)-L-OddC and STI571 (Brief, page 5, paragraph 7). However, contrary to Appellant's assertion, the Examiner has clearly set forth the teaching, suggestion, and motivation to combine these two agents for the treatment of leukemia as set forth *supra*. In this regard, Chu *et al*. explicitly teach that (-)-L-OddC can be combined with another agent for the treatment of cancer and Fang *et al*. and Topaly *et al*. explicitly teach that STI571 is effective

when combined with other agents for the treatment of leukemias. As such, given the proven efficacy of both (-)-L-OddC and STI571 for the treatment of leukemias in human patients, the skilled artisan would have been imbued with at least a reasonable expectation that these agents, when combined, would also be effective for the treatment of leukemias.

Appellants further argue that the disclosures of Fang *et al.* and Topaly *et al.* do not establish that one skilled in the art would expect STI-571 to exhibit synergy with every anti-leukemic agent (Brief, page 7, paragraph 2). In this regard, Appellants argue that the structures of cytarabine (Ara-C), etoposide, doxorubicin, and mafosfamide [compounds taught to be synergistic when administered with STI571 in Fang *et al.* and Topaly *et al.*] are all clearly distinguishable from that of (-)-L-OddC (Brief, page 7, paragraph 3). However, given the fact that such structurally divergent compounds all exhibit synergism when administered with (-)-L-OddC, the skilled artisan would have reasonably expected that such synergism would also occur when STI-571 is administered with (-)-L-OddC for the treatment of leukemia because the mechanism of action of STI-571 (inhibition of Bcr-Abl tyrosine kinase) does not change when it is administered with different compounds having different structures as evidenced by the synergism observed with structurally distinct agents.

In response to Appellant's argument that the synergism demonstrated in the specification is unexpected (Brief, page 6, paragraphs 3-6, citing specification at pages 25-28), even if the Examiner were to accept that such results are indeed unexpected, which he does not for the reasons given above, the experimental results in the specification are not commensurate in scope with the claims. For example, the claims recite compositions and methods comprising

compounds of Formula (I) having any stereochemistry, in any amounts, to treat any type of leukemia, in combination with any amount of STI-571, provided that the compounds are present in a ratio of 1:5 to 1:2. However, Appellant's results are limited to the effects of a specific combination of Troxatyl and STI-571, in doses of 10 mg/kg or 50 mg/kg "Troxatyl" administered qd x 5 (every day for 5 days) and 50 mg/kg STI-571 administered bid x 10 (twice a day for 10 days) for the treatment of chronic myeloid leukemia. Accordingly, the Examiner is not persuaded that Appellants have demonstrated unexpected synergistic results commensurate in scope with the patent protection sought.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Examiner, Art Unit 1614

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